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Copolymers of lactic and glycolic acids have been traditionally synthesized by the copolymerization of lactide and glycolide, which are cyclic dimers of lactic and glycolic acids, respectively. When these two monomers are copolymerized by ring-opening polymerization, the result is a random diad of glycolic and lactic acids. Furthermore, due to the different reactivities of the two comonomers, glycolide- and lactide-rich regions would result in addition to the random regions. These problems cause the polymer to have variability in their properties from batch-to-batch. Also, by making the polymer more random, the polymer will not be able to crystallize.

To synthesize an alternating copolymer of lactic and glycolic acids requires a monomer that is a hybrid of lactide and glycolide. This monomer is called 3-methylglycolide or 3-methyl-1,4-dioxan-2,5-dione according to IUPAC nomenclature. Three approaches were attempted out of four proposed routes. The most viable route involved the reaction of sodium glycolate with 2-bromopropionyl bromide.

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SYNTHESIS OF POLY(LACTOYL GLYCOLATE): AN ALTERNATING COPOLYMER OF LACTIC AND GLYCOLIC ACIDS

FINAL REPORT

AUGUST 1987

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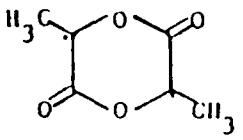
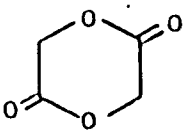
SYNTHESIS OF POLY(LACTOYLGLYCOLATE): AN ALTERNATING COPOLYMER OF LACTIC AND GLYCOLIC ACIDS

INTRODUCTION

Copolymers of lactic and glycolic acids have been traditionally synthesized by the copolymerization of lactide and glycolide. These comonomers, with the structures shown, are cyclic dimers of their respective organic acids.



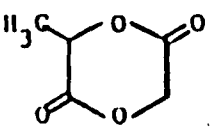
lactide



glycolide

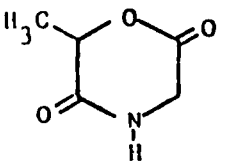
Due to their structural differences, there exists a difference in their reactivity. Thus, for example, in the synthesis of 50:50 poly (lactide-co-glycolide), more lactide than glycolide is added in the reaction mixture because glycolide is more reactive with itself than with lactide.[1] By increasing the amount of lactide, the thermodynamics for the production of the desired polymer composition becomes more favorable. Nevertheless, the resulting copolymer is always a random one with variable glycolide and lactide rich regions along the chain. Because of this variability, the properties of the polymer also become a variable with each synthesis. These properties include solubility, drug-release, degradation rate, and molecular weight.

A literature search indicates that there is a patent for the synthesis of the alternating copolymer of lactic and glycolic acids.[2] The copolymer is produced by polymerizing 3-methylglycolide, whose structure is shown below.



This monomer is a hybrid of lactide and glycolide. Although the patent was awarded to the inventors in 1977, the polymer is not presently commercially available. This raises suspicion on the reproducibility of the synthesis of the monomer and/or the alternating copolymer. Since there are studies reported on the homo-polymerization of lactide and glycolide[3-6] and their co-polymerization with either each other or other lactones[7, 8] the mechanism of these ring-opening polymerizations is well understood. Although a proposal has been submitted to USAIDR to optimize the conditions for producing copolymers of lactide and glycolide that have consistent properties from batch-to-batch,[9] the root cause of the batch-to-batch variability was not addressed. Therefore, it has become the objective to reapproach the synthesis of 3-methylglycolide.

Long after the publication of the referenced patent, Feijen reported the synthesis of 3-methyl-morpholine-2,5-dione in 1985.[10] *This compound with the* structure below,



is an isostere of 3-methylglycolide and a cyclic derivative from glycine and lactic acid. Upon polymerization under the same conditions as the polymerizations of lactide and glycolide, the product is an alternating copolymer of glycine and lactic acid.[11]

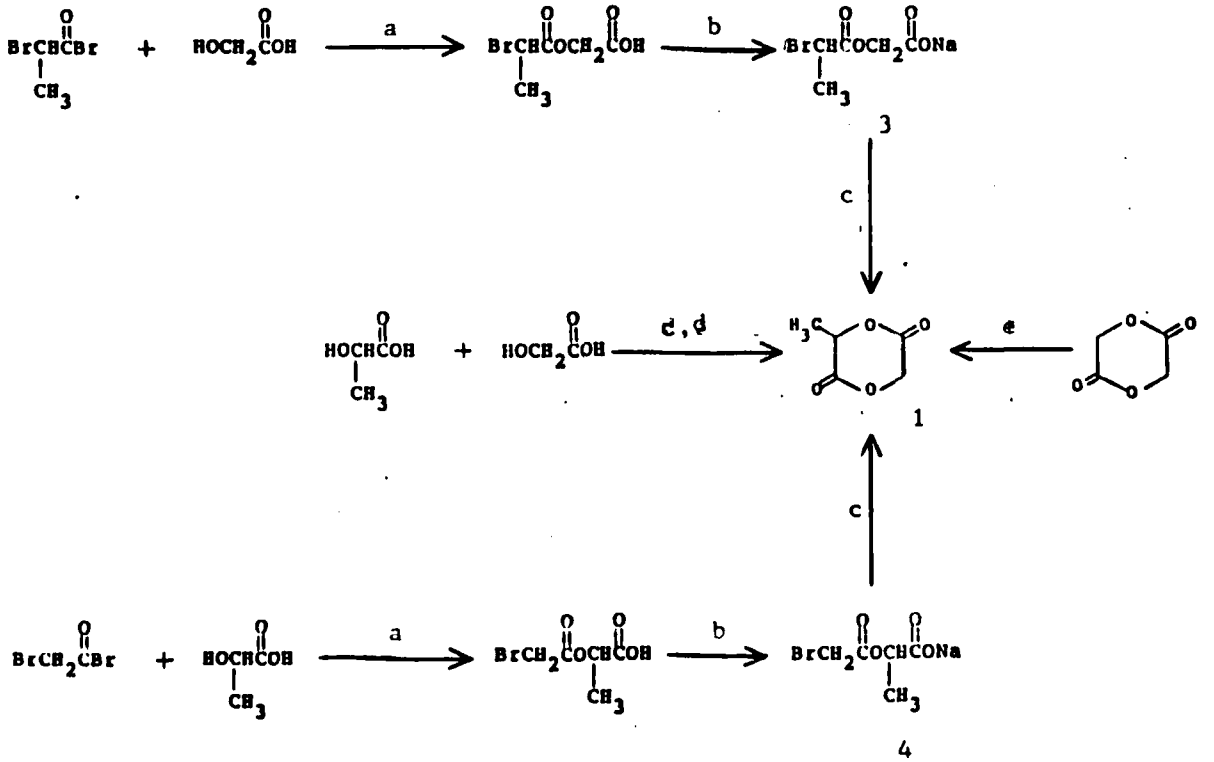
Further evidence from ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy of poly(d,l-lactide) indicates an alternating sequence of d- and l-lactic acid.[12, 13] Since d,l-lactide and the targeted monomer have similar functionalities, fundamentals of organic chemistry suggest that the mechanism ofpolymerization should be identical. Therefore, the polymerization

of 3-methylglycolide under similar conditions, should result in an alternating copolymer of lactic and glycolic acids.

Several synthetic approaches to the monomer have been proposed (see Scheme 1). Two of the routes involve acylation and cyclization reactions. One of these two routes reacts 2-bromopropionyl bromide with sodium glycolate. The other route reacts chloroacetyl chloride with calcium lactate. The intermediate from either route is subsequently neutralized and then thermally cyclized. The third route is a polycondensation that results in a low molecular weight copolymer which is subsequently thermolyzed. The last route is a methylation of glycolide.

SCHEME 1

APPROACHES TO 3-METHYLGLYCOLIDE



a, $(C_6H_5)N(CH_3)_2$; b, NaOH; c, heat; d, Sb_2O_3; e, CH_3I, NaH.

EXPERIMENTAL

MATERIALS. The chemicals whose commercial sources are not given were purchased from Aldrich Chemical Co. The 2-bromopropionyl bromide was purified by fractional distillation under aspiration.

INSTRUMENTATION. NMR spectra were recorded on an IBM NR300AF FT-NMR spectrometer. Chemical shifts are reported relative to Me_4Si. GC/MS spectra were recorded on a Finnegan Model 4500 quadrupole mass spectrometer and a Finnegan Model HSQ-30 Hybrid Tandem mass spectometer.

MONOMER SYNTHESIS.

1. Acylation-Cyclization Methods. Method A: Sodium glycolate was produced by titrating a saturated solution of 97% glycolic acid in ethanol with subsequent isolation of the product by vacuum filtration of the precipitate and drying it in the vacuum oven to a constant weight. Under dry nitrogen, approximately 500 grams of purified 2-bromopropionyl bromide was chilled to 0°C in an ice bath. With mechanical stirring, 1.0 mole of the powdered sodium glycolate was added portionwise such that the mixture temperature remains between 0 and 10°C. When the addition was completed, the ice bath was allowed to melt to bring the temperature to ambient conditions while mechanical stirring was allowed to continue for 24 hours. The mixture was then vacuum filtered through a medium fritted glass funnel with the aid of Celite. The filtrate was fractionally distilled under vacuum to isolate the product, 2-bromopropionyl glycolate, as a clear colorless, slightly viscous liquid. The yield was approximately 80% based on the amount of sodium glycolate used. The cyclization step was carried out as follows: a 60% sodium hydride dispersion in oil was suspended in dry tetrahydrofuran which had been chilled in an ice bath. One equivalent of the 2-bromo-propionyl bromide was added drop-wise under dry nitrogen and with mechanical stirring. Evolution of hydrogen gas was noted. After 24 hours

of continued stirring at ambient temperatures, the solvent was rotary evaporated. The remaining sodium salt was heated to 200°C under vacuum to afford small amount distillates of the compound of interest. Chemical analysis by the addition of 0.1 N solution of silver nitrate to a dilute ethyl acetate solution of the suspected product was negative for a silver bromide precipitate. An ethyl acetate solution of the starting material, which was positive for the silver halide test, was the control. NMR analysis also confirmed the structure as shown by the spectrum in Figure 1. Note the doublet at 1.92 ppm, the singlet at 3.92 ppm, and the quartet at 4.46 ppm which correspond to the methyl, methylene, and methine, respectively.

Method B. Calcium lactate pentahydrate was dried in a vacuum oven at 50°C in the presence of phosphorous pentoxide to a constant weight. Chloroacetyl chloride was synthesized by refluxing chloroacetic acid in pre-distilled thionyl chloride and distilling the reflux mixture after 24 hours. Chloroacetyl chloride was isolated at 105°. The procedure for reacting calcium lactate and chloroacetyl chloride was identical to Method A. The product isolation method was also the same.

2. Direct lactate-glycolate Condensation. A mixture consisting of 80 g (1.05 mol) of glycolic acid, 120 g of 80% lactic acid (1.06 mol), and 0.17 g (0.58 mmol) of Sb_2O_3 in a 500 mL 3-neck round bottom flask was heated with a heating mantle while mechanically stirring. The stirrer was connected to a gear box which was powered by a stirrer controller. The stirrer rate was set to 60 rpm and the temperature was gradually increased until water began to distill under aspiration. As water distillation subsided, the temperature was increased up to 180° and maintained at this temperature for at least 18 hours. The mixture was then cooled after removing the mechanical stirrer and the apparatus was retro-fitted for simple vacuum distillation in which a series of two dry ice

traps were used to collect the distillates. Vacuum was applied to 0.3 mm Hg and the reaction was heated to 250°C. The product collected in the first dry ice trap and was submitted to MS analysis.

RESULTS AND DISCUSSION

To date, three of the four routes for producing the monomer have been attempted. Of the two acylation-cyclization methods, Method A was the more successful. In Method B, only the starting materials were isolated upon work-up. It is apparent that heating may be required in Method B in order to displace the chloride at the alpha-carbon. In Method A, the acylation step of the two-step route readily proceeded at ice-cold temperatures due to the higher reactivity of an acid bromide. GC/MS analysis confirmed the presence of bromide as indicated by peaks at 79 and 81 atomic mass units. The mass spectrum is shown in Figure 1. The molecular peak was not easily distinguishable, but the degradation products at 197, 195, 193, 181, 179, 153, 151, 137, 135, 116, 114, 109, and 107. The degradation pathway is shown in Figure 2.

After the intermediate was purified, it was cyclized according to the procedure prescribed earlier. When the sodium hydride reacted with the acid, hydrogen gas was liberated and a white gummy precipitate immediately appeared. After work-up, the procedure that followed was similar to the technique used in the synthesis of glycolide[14] or lactide.[15] After the isolation of the product by vacuum distillation, an odor was noted which was similar to that observed at the same step in the synthesis of lactide or glycolide. Yield was low, and the compound was hygroscopic. Chemical analysis by silver nitrate test was negative for a halide. The NMR spectrum confirmed the structure of the product, but also indicated the presence of impurities. The NMR spectrum is shown in Figure 3.

FIGURE I

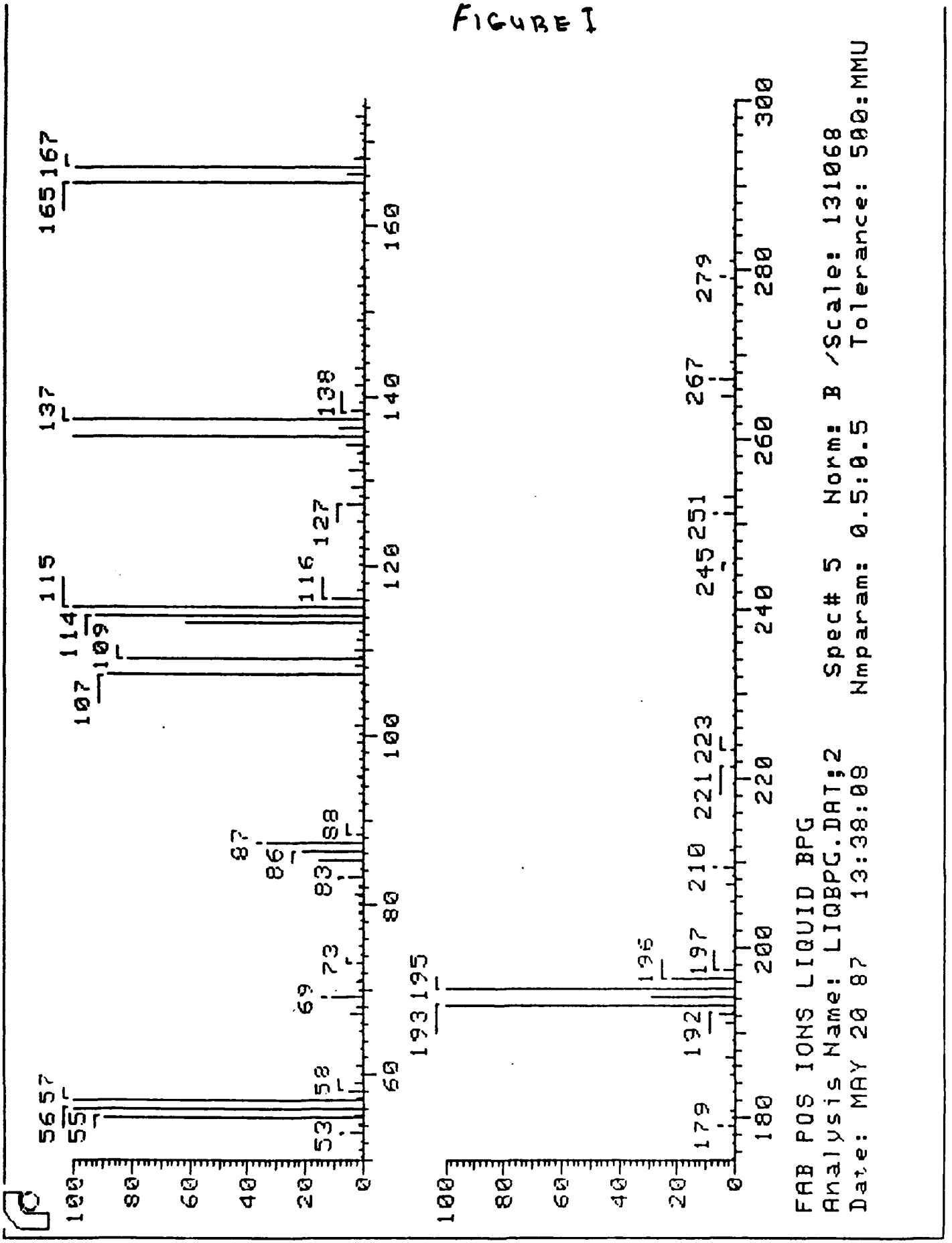

FAB POS IONS LIQUID BPG
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FIGURE 2

FRAGMENTATION PATTERN OF 2-BROMOPROPIONYLGLYCOLATE

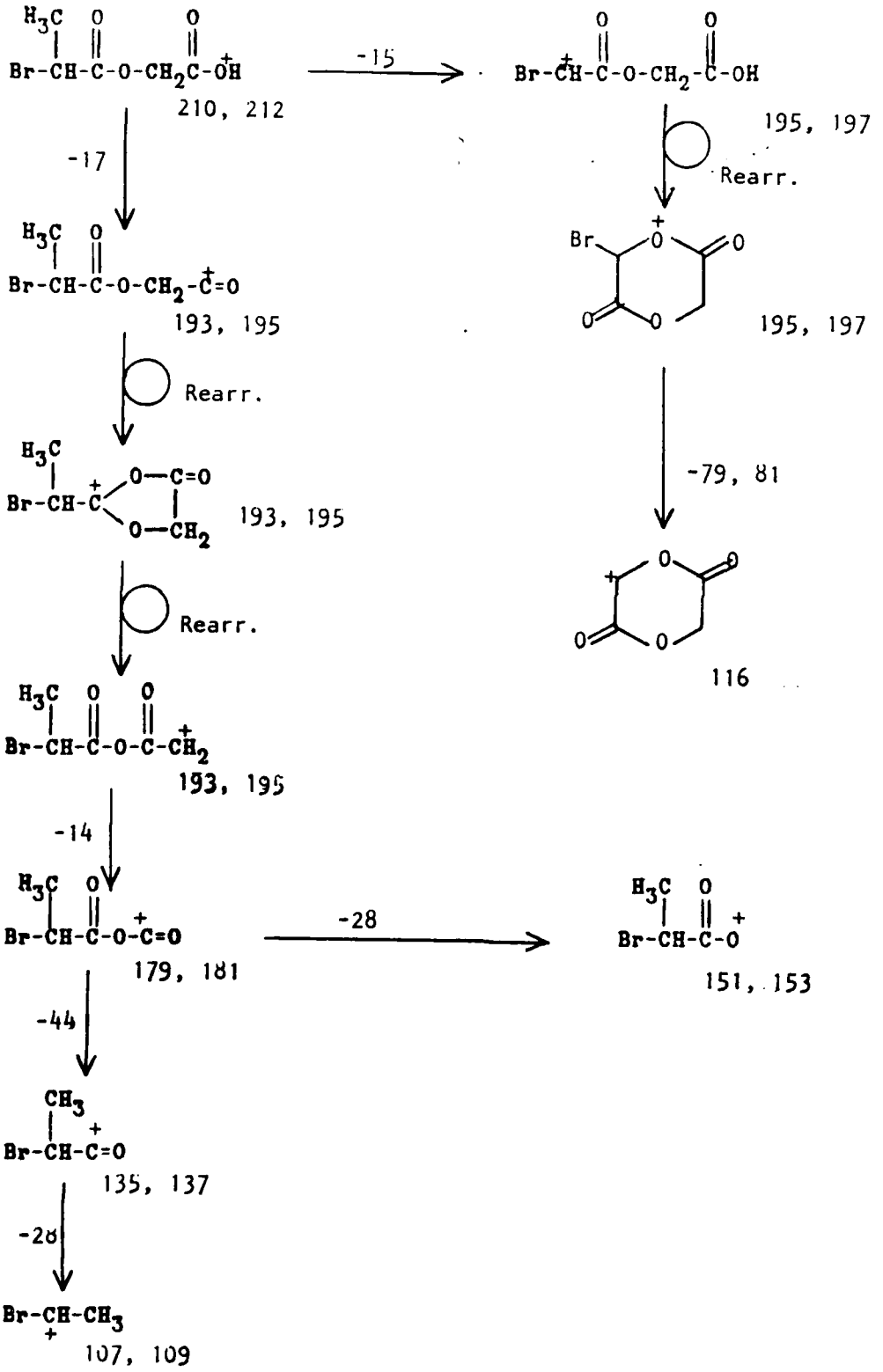
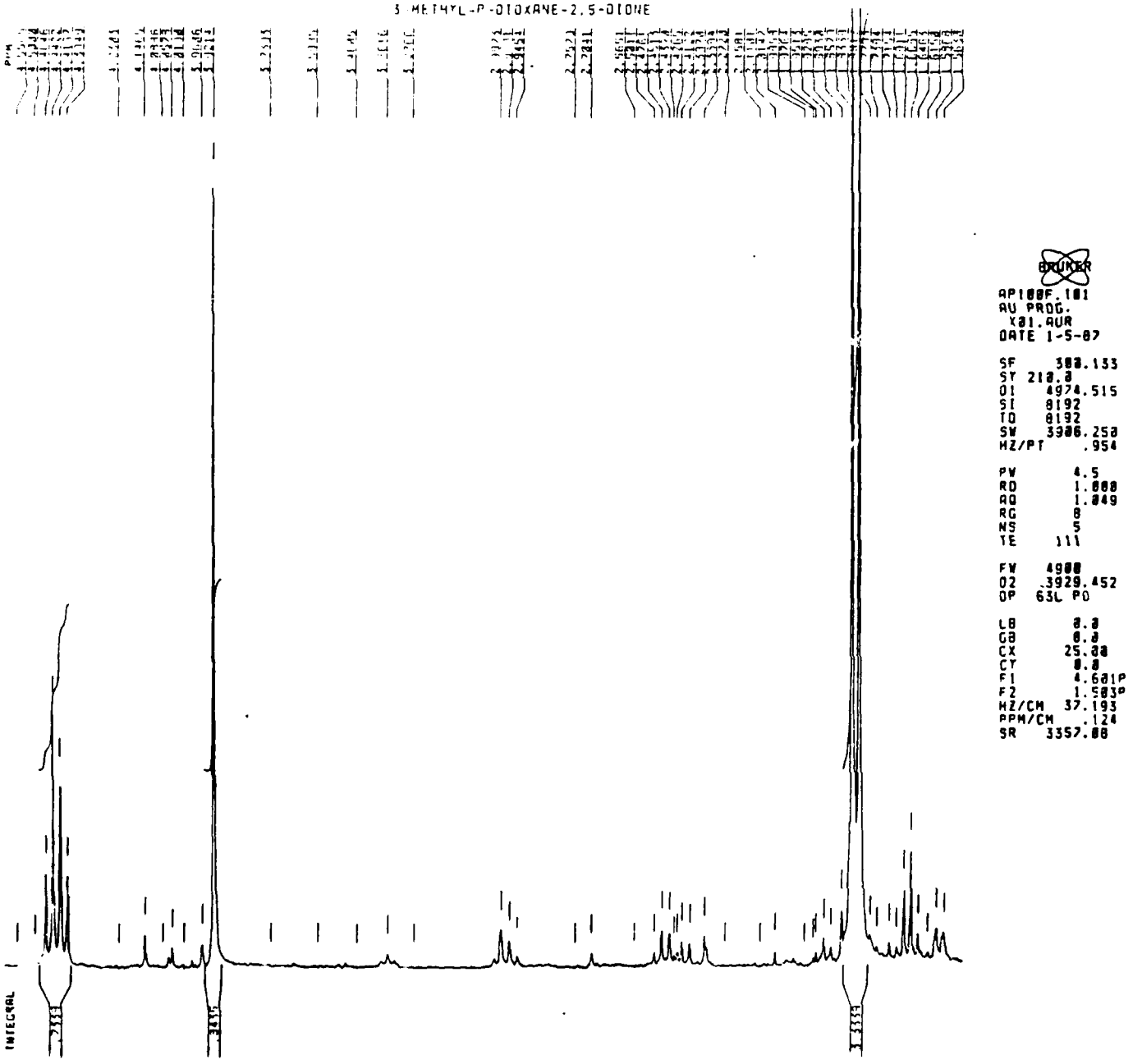


FIGURE 3


3 METHYL-P-DIOXANE-2,5-DIONE
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SF 300.133
SY 210.0
OI 4974.515
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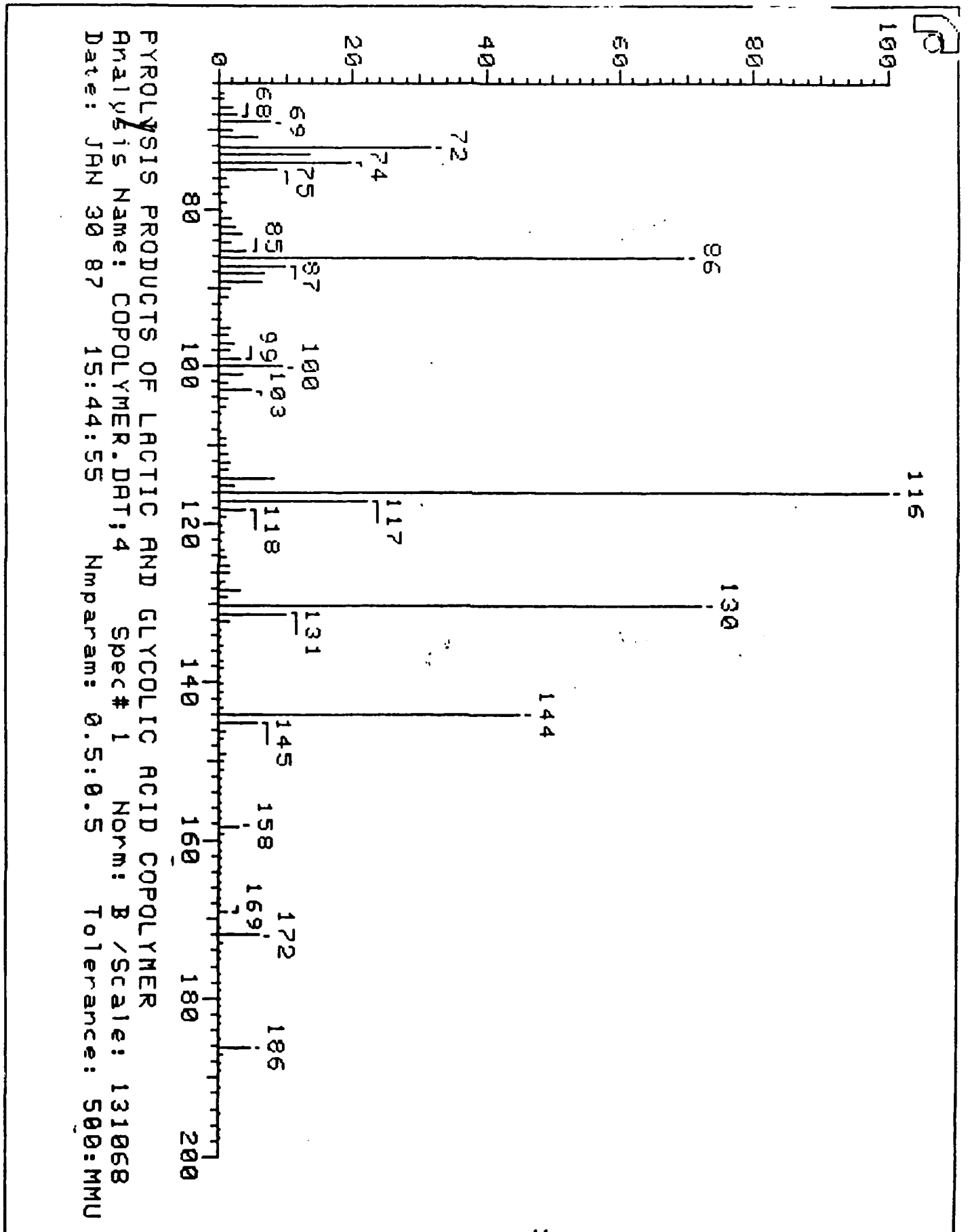
TD 8192
SW 3906.250
HZ/PT .954
PW 4.5
RD 1.000
AQ 1.049
RG 8
NS 5
TE 111
FW 4900
O2 3929.452
OP 63L PO
LB 0.0
GB 0.0
CX 25.00
CY 0.0
F1 4.601P
F2 1.503P
HZ/CM 37.193
PPM/CM .124
SR 3357.88

The method using both lactic and glycolic acid as starting materials was shorter, but it resulted in a mixture of products. This is acceptable only if the desired product is the major one. However, this was not the case. It was determined that three products formed, which were lactide, glycolide, and the 3-methylglycolide. The reaction conditions were designed such that, at best, lactic and glycolic acid would be equally reactive towards each other. Under such conditions, the theoretical product ratio would have been approximately 1:1:1. It in unknown at this stage if the reaction yielded this composition. The mass spectrum of this mixture is shown in Figure 4. The peak intensities of the three monomers at 116 (glycolide), 130 (3-methylglycolide), and 144 (lactide) mass units are different and should not be miscontrued to be the ratio of the reaction products. Separation of the three products was not attempted because it was not practical to isolate the product when the yield for this synthesis was already low (<20%). It should be noted also, that although the synthesis is identical to the procedures used in lactide and glycolide synthesis, a possible decomposition may have been occurred which was evidenced by the darkening of the mixture during the initial dehydration step. Thus, this approach may not be practical in the production of 3-methylglycolide.

CONCLUSIONS

A probable reason for the lack of commercialization of an alternating copolymer of lactic and glycolic acids, despite the presence of a chemical patent, is the instability of the intermediates in the reaction to synthesize the 3-methyl glycolide. In all the reactions that led to the isolation of the product, some type of decomposition of an isolated intermediate or in the reaction was observed. This was evidenced by the darkening of the intermediate or of the reaction mixture, respectively. At this stage in the

FIGURE 4


PYROLYSIS PRODUCTS OF LACTIC AND GLYCOLIC ACID COPOLYMER
Analysis Name: COPOLYMER.DAT;4 Spec# 1 Norm: B /Scale: 131068
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186

development of the alternating copolymer, it is not yet conclusive whether the proposed routes are viable. If the decomposition reactions are oxidations or reductions, there are redox inhibitors available to counteract these side reactions.

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